## *IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

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| Applicant: | HAYWOOD et al. |
| Title: | METHOD AND APPARATUS FOR DETERMINING EFFECTIVENESS OF SUNSCREENS AND OTHER SKIN PREPARATIONS IN SHIELDING HUMAN SKIN FROM UVA RADIATION |
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Sir:

**DECLARATION PURSUANT TO 37 C.F.R. 1.132**

I, Rachel Mary Haywood, hereby declare as follows:

1. I am the first named inventor in this patent application. I hold an honours degree in Chemistry from York University, England, and was awarded a doctorate (PhD) by York University, England in 1992. My post-doctoral research was at the Royal London Hospital Medical College and Queen Mary and Westfield College, London University, England. My area of research is the study of skin damage by ultraviolet light and the role of free radicals in skin cancer. I have held the position of Group Leader in Free Radical Research at the assignee RAFT since 2004.

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2. I have studied the Office Action of March 20, 2008 and note that claims 1-8 and 15-17 are rejected as claiming subject matter that was obvious over Jurkiewicz et al Photochemistry and Photobiology, 1996, 64(6), 918-922 in view of Robinson, US Patent 5,968,485. I disagree with this rejection, for the following reasons.

3. I disagree with the examiner's summary of Jurkiewicz et al in the passage bridging pages 4 and 5 of the detailed comments of the Office Action. This passage reads as follows:

> "Jurkiewicz et al teach EPR (i.e., ESR) detection of ascorbate free radicals in UV-irradiated skin (see abstract). A sample of human skin was irradiated with UV radiation comprising UVA wavelengths, either unshielded or shielded with a shield such as a filter (see page 919, third full paragraph), and the ascorbate radical EPR signal was determined. Jurkiewicz et al. also teach irradiating a sample to which the photoprotective agent Desferal has been topically applied, and with which a 305 nm UV cutoff filter was used (page 921, first paragraph)".

4. The filters described at page 919, third full paragraph are to provide radiation in only the selected portions of the spectrum, as stated in the legends to Figures 1 (mouse skin) and 2 (human skin). The data in those Figures were obtained using (i) radiation containing both UV (A and B) and visible light (to mimic solar radiation) (■) and (ii) visible light only (no UV or IR) (▲), according to the filters used.

5. Therefore, it is not correct to say that a sample of human skin was irradiated with UV radiation comprising UVA wavelengths, **either unshielded or shielded with a shield such as a filter.** In Figure 2, when UVA wavelengths were present (in the experiment to examine solar radiation (■)) the only human skin used was unshielded because the filter **allowed the passage of the UVA radiation** from the lamp, and therefore could not act as a shield. The other data in Figure 2 related to visible light only (▲), so in that case there was no UVA radiation on the skin.

6. In the Desferal experiment (Figure 5), Jurkiewicz et al irradiated human skin with the UV-and-visible light (to mimic solar radiation). Jurkiewicz et al describe Desferal as

a "photoprotective agent", but make it clear (passage bridging pages 920-921) that it is so described because it is an iron chelator and in the mouse model topical application of iron chelators to skin has been found to be "photoprotective by delaying the onset of UV light-induced skin tumor formation". Jurkiewicz et al specifically point out in that passage that Desferal has no significant UV absorption at wavelengths greater than ≈ 280nm, and thus **would not act as a simple UV blocking agent** when the 305 nm UV cutoff filter is used.

7. Jurkiewicz et al confirmed (Figure 5) that the **UV-non-blocking** iron chelator Desferal did decrease EPR spectral signals from Asc$^{\bullet}$ and DMPO spin-trapped radical adducts in human skin on exposure to the solar-mimicking radiation (containing both UV (A and B) and visible light), and explained it in the main paragraph of column 2 of page 921. In that passage, Jurkiewicz et al concluded that they favoured an iron sequestration mechanism, in which non-heme iron of a person's skin is sequestrated by the Desferal. [As stated in column 2 page 920 chronic exposure of human skin to UV radiation has been found to increase basal levels of non-hemoglobin iron]. The iron released by UVA catalyses lipid peroxidation in the non-chelated form but not in the chelated form, and this catalysis is prevented by Desferal. This is a different mechanism of photoprotection than that which would be afforded by a UVA filter which reduces the quantity of radiation reaching the skin. Jurkiewicz et al add that the absence of aminoxyl radicals suggests Desferal is chelated to free iron and supports an iron sequestration mechanism. Jurkiewicz et al clearly attribute the Desferal-induced decrease in EPR spectral signals to this special property of Desferal, which counteracts the tendency for non-heme iron (released by UV effects in the skin) to generate radicals on exposure to UV.

8. The Examiner is therefore not correct to suggest that the replacement of one "photoprotective" (Desferal) by another (the Robinson sunscreen) was obvious. The

Desferal experiment in Jurkiewicz et al was clearly a special study to see whether the known mouse result held in human skin and was not in any way seeking to show that the effects of shielding human skin from UVA radiation could be quantitatively measured using ESR. The Desferal experiment **used UVA** to irradiate the Desferal-coated skin, in other words **deliberately failed to shield the Desferal-coated skin sample from UVA**, to see what the result would be as a means for studying the interaction of the iron chelator with skin heme iron. It cannot be conceived from this Jurkeiwicz et al work that it would lead obviously to any method for quantifying the result of deliberately using a sunscreen to shield the skin sample from UVA. All that Robinson provides is a sunscreen. He says nothing that would rectify the deficiencies in Jurkiewicz et al as a means for getting obviously to the invention. In particular, Robinson does not provide a pointer to use ESR (or any other technique, in fact) to examine **sunscreen-UVA-shielded** skin, as a way of seeing **how effective** the sunscreen is against UVA radiation.

9. As well as the fact that the Jurkiewicz et al are interested only in looking at **unshielded** skin in their UVA exposure experiments, their work completely lacks the **quantitative** element involved in the invention of this application.

10. In the Jurkiewicz et al study, as mentioned above, skin was exposed to either broad band UV and visible light (using a 305 nm cut-off filter) or visible light only (using a 400 nm cut-off filter) and the ascorbate radical signal height monitored as a function of time for each wavelength band independently of the other. The cut-off filters are used solely as a device to generate different wavelength bands with which to irradiate the human skin, and were not used with the intention of providing a protective screen to shield the skin, to determine the relative reduction in ascorbate radical signal. It is seen in Jurkewicz et al's data (Figures 1 and 2) that, by removing part of the spectrum (i.e. UVA wavelengths), there is some reduction in the ascorbate radical signal intensity.

However, there is no indication that this is a quantitative reduction in proportion with the reduction in radiation exposure. The data compares two different wavelength bands, where the quantum yield of ascorbate radical generation may vary. Thus, it cannot be assumed that there will be a proportionate reduction in signal intensity when comparing different wavelength regions, only that there is a relative contribution of each region to the ascorbate radical signal.

11. Furthermore, Jurkiewicz et al do not state how the ascorbate signal height for Figures 1 and 2 was measured. This lack of information prevents the reader from extending the Jurkiewicz et al work to differential skin radical quantification where ESR spectra from more than one skin sample are compared quantitatively. Firstly, where both samples are biological samples they are subject to all the normal variability found in biological systems. Secondly, the ESR signal is a first derivative absorption measurement (not a direct absorption measurement). Even without the problems associated with variability of biological systems, prior to the present invention first derivative spectral measurements were considered less reliable than direct measurements for quantification, because of the need to perform a mathematical integration of the spectral data as part of the quantification. Thirdly, Jurkiewicz et al do not discuss the rates of the radical formation and decay processes, that are relevant to the height of the radical signal. A relative quantification cannot be performed unless the amount of the radical is known to be constant over at least a certain time period. In the present invention we found, unexpectedly, that in fact the ESR technique can be used in a differential manner to quantify skin radicals and thereby to measure the effectiveness of sunscreen compositions as described.

12. I disagree with the Examiner's inference from the passage on page 14 of the specification. On page 6 of the detailed comments of the Office Action, the Examiner comments as follows:

> "Regarding the step of determining a quantitative measure of the effectiveness of the sunscreen composition in reducing the exposure of human skin to UVA radiation, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to compare levels of ascorbate radical production in the shielded and reference skin samples. Comparing the data obtained between a sample and its comparable reference is generally conventional and well within the capacity of one of ordinary skill in the art, as substantiated by the Applicant's remarks on page 14 of the specification".

The relevant passage on page 14 reads as follows:

> "The means for determining a quantitative measure of the effectiveness of the sunscreen composition or other skin preparation in reducing the exposure of human skin to UVA radiation, by comparison of the levels of ascorbate radical production in the shielded and reference skin samples, preferably comprises electronic signal processors and conventional associated electronic apparatus adapted to measure the differential signal height between the samples and to display the result as a readout and/or printout in generally conventional manner. The provision of such apparatus and associated controlling software will be well within the capacity of one of ordinary skill in this art, and does not require further explanation".

This passage therefore merely states that **providing the apparatus**, *once one has been told of the invention*, is within the capacity of the ordinary skilled reader. It certainly does not say that it is obvious to go from Jurkiewicz et al and Robinson to the present invention. For the reasons elaborated above, there is nothing in Jurkiewicz et al or Robinson, whether read alone or together, to suggest to the reader of ordinary skill in the art that the ESR technique could successfully be applied quantitatively to analyse the UVA screening effectiveness of sunscreen compositions or other skin preparation.

13. Specifically, it is wrong to suggest that "comparing the data obtained between a sample and its comparable reference is generally conventional" in this art. Prior to the present invention, there was no understanding that ESR data could be used comparatively and quantitatively in the way of the present invention, and it is my firm belief that this was not obvious. The EPR (ESR) data obtained by Jurkiewicz et al were expressed in arbitrary units only when the results from unrelated experiments

using uncomparable radiation were plotted together (Figures 1 and 2), or were entirely unquantified (Figures 3 to 5). There was no suggestion of comparative quantifiability in Jurkiewicz et al, and this deficiency was not addressed at all in Robinson.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

19th September 2008
Dated

Rachel Haywood
Rachel Mary Haywood